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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/980,038	11/26/97	KAUFMAN R	211500118 4US

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EXAMINER	
CELSA, B	
ART UNIT	**PAPER NUMBER**
1654	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.	Applicant(s)
08/980,038	Kaufman et al.
Examiner	**Group Art Unit**
Bennett Celsa	1654

☒ Responsive to communication(s) filed on *Apr 21, 1999*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *17-23, 27, 32, 36, and 102-147* is/are pending in the application.

Of the above, claim(s) *18, 19, 32, 36, 102-106, 108, 109, 114-119, and 121* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *17, 20-23, 27, 107, 110-113, 120, 146, and 147* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Applicant's amendment dated 4/21/99 is acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 17-23, 27, 32, 36 and 102-147 are currently pending (claims 146 and 147 are newly added)..

Claims 18-19, 32, 36, 102-106, 108-109, 114-119 and 121-145 are withdrawn from consideration as being directed to a nonelected invention.

Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are under consideration.

Sequence Rule Compliance

Applicant's Sequence listing submitted on 2/4/99 has been received and entered.

Withdrawn Objection(s) and Rejection(s)

The indefinite rejection in items G. and H. of the prior office action have been overcome by applicant's amendment.

Outstanding Objection(s) and Rejection(s)

2. Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 17 and 107, the structure of the human factor FVIII polypeptide which is modified to attain the "procoagulant-active FVIII protein) is indefinite. One needs to know the starting point (e.g. the initial polypeptide structure) in order to determine a final product which would infringe or not infringe the claim. Thus, the metes and bounds of the final protein are not known if the metes and bounds of the starting polypeptide are not described.

B. In claims 17 and 107, the term "the B domain" lacks antecedent basis.

C. In claims 17 and 107, the term "the von Willebrand factor binding site" lacks antecedent basis.

D. In claims 17 and 107, the term "the A2- and A3- domains" lack antecedent basis.

E. In claims 17 and 107, the phrase "a mutation at Arg740" lacks metes and bound as to what the metes and bounds of such mutations are. Do mutations include a deletion of Arg740 ? Only substitutions of Arg740 ? A covalent modification of the Arg amino acid (e.g. sidechain, peptide bond, hydrogen)? The nature of the mutation (e.g. natural or man-made) is unclear.

F. Claim 22, 23, 112, 113, 146 and 147 the phrase "comprises residues 741 to 794 of wild-type factor FVIII... " and "position 794 ... threonine (and leucine) lacks clear antecedent basis since claims 17 and 107 which require deletion of the B-domain which would include these amino acid residues. Additionally, with respect to new claims 146 and 147, "comprising" would encompass the entire B-domain which is contradictory to the claimed absence of the B-domain.

Discussion

Applicant's arguments directed to the above indefinite rejections were considered but deemed nonpersuasive for the following reasons.

In response to item a. above applicant argues that the term "procoagulant-active FVIII protein" is clear citing prior issued patents in support and the specification disclosure of DNA

sequences encoding human FVIII protein. However, the Examiner is confused with the starting structure that is used to derive the "procoagulant-active FVIII protein". This is confusing to the Examiner since the claim recites "a human Factor VIII polypeptide that is modified" which implies that there is multiple human factor VIII polypeptides which may be the human form or some other modification thereof. Simply amending to delete "a" would clarify the scope of the claim to be consistent with applicant's argument and the disclosure.

With respect to items B)-D) above, applicant argues that human factor VIII protein is well known in the art. Applicant's argument will have merit upon clarification of the above item a. issue. Until then the above rejections for improper antecedent basis are retained, since the starting material (e.g. a human Factor VIII polypeptide that is modified) is still indefinite and thus incapable of providing proper antecedent basis. Additionally, it is noted that chemical structure which is necessary for claim interpretation (e.g. the various regions of human factor VIII) should be in the claim, since the Examiner cannot read critical claim limitations into the claim and applicant is under a duty to provide a clear indication as to what chemical structure will or will not infringe the presently claimed invention.

With respect to item E) above applicant argues that the term "mutation" refers to any alteration including but not limited to, substitutions, insertions and deletions citing the specification on page 10, lines 25-26 and Example 3 showing a single Arg740 mutation. However, the specification definition is clearly open ended (e.g. " including but not limited to") and thus is not strictly limited to "substitutions, insertions and deletions". Additionally, there is no

recitations as what chemical entity or entities are substitutable or insertable at the Arg740 position nor are the possible substituents limited in length, conformation, chemical properties or any other parameter. The demonstration of a single amino acid substitution (e.g. Example 3) does not serve to limit the metes and bounds of the presently claimed invention. Additionally, it is further unclear as to how such a mutation occurs.

With respect to item F. above applicant argues that the claimed human FVIII although B-domainless can nevertheless contain a portion of the B-domain which is a called a linker. Applicant's argument is misguided. For use of the term "comprising" in new claims 146 and 147 would encompass the entire B-domain, forcing applicant to argue that the claim encompasses a protein which is both B-domainless but yet also contains a B-domain. The claimed language is clearly confusing since it requires the absence of the B-domain, yet applicant's depended claim encompasses the partial to total presence of such a domain regardless of how it is labeled (e.g. as a linker or otherwise).

With respect to item G. above it is noted that this rejection, although no longer applicable to claims

3. Claims 146 and 147 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The phrase "comprises residues 741 to 794 of wild-type factor FVIII... " and "position 794 ... threonine (and leucine)" which include B-domain amino acid residues (up to the entire B-domain) fail to limit claims 17 and 107 that requires deletion of the B-domain. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. .

Discussion

Applicant's argument and amendment were considered with regard to the above revised objection, but deemed only partially persuasive with respect to claims 22-23 and 112-113 only. It is noted that the above objection was modified in response to applicant's amendment which added new claims 146 and 147. Applicant has failed to present a persuasive argument as to how a B-domainless generic claim is narrowed by dependent claims which encompass B-domain containing peptides.

Claim Rejections - 35 USC § 102

4. Claims 17, 27, 107 and 120 are rejected under 35 U.S.C. 102(b) as being anticipated by WPIDS English Abstract 88-362113 or EP 295597 (12/88) (which is attached for applicant's convenience).

The EP reference discloses a factor 8 derivative compound and its preparation in pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689: wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The reference further discloses that "the new

protein possesses a rapid activation by thrombin aside from a procoagulation activity that is very smililar to one of the authentic protein and biologic half-value time" (e.g. see translation at page 2, lines 9-12). Thus the reference protein is stable and possesses a good specific activity. Accordingly, the reference meets the critical chemical claim limitations (e.g. absence of a B domain and Vwf binding site; and presence of a linking amino acid) and possesses improved properties and thus would be expected to "inherently" possess the same conformational structure upon thrombin activation as presently claimed. See MPEP 2112.02 and *In re Spada*, 15 USPQ2d 1655,1658 (Fed. Cir. 1990)("Products of identical chemical composition can not have mutually exclusive properties"). The Examiner lacks the facilities to test the reference protein to see if it meets functional limitations; thus placing the burden directly on applicant (e.g. See *In re Brown*, 173 USPQ 685,688 (CCPA 1972)) .

Discussion

Applicant's arguments directed to the above rejection were considered but deemed nonpersuasive for the following reasons. Initially it is noted that the above rejection was modified in response to applicant's amendment. Applicant argues that the reference fails to disclose a "spacer". However, the reference clearly teaches a protein which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. Thus, chemically the reference compound meets the presently claimed spacer limitation. Applicant argues that the reference fails to disclose both a mutation at Arg 740 and an amino acid sequence spacer. However, the reference clearly does teach a mutated Arg-740 which acts an

amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. Accordingly, the reference discloses a protein that contains all the elements of the presently claimed invention. The presently claimed invention does not preclude the interpretation that the mutated amino acid can also serve as the spacer. With regard to to applicant's functional/conformational limitation language it is noted that functional activity would inherently flow from a compound that possesses chemical structure within the scope of the presently claimed invention; unless demonstrated otherwise. Accordingly, the above rejection, as modified, is hereby retained.

Claim Rejections - 35 USC § 103

5. Claims 17, 20-22, 27, 107, 110-112, 120, 146 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over WPIDS Abstract 88-362113 of EP 295597 (or translation thereof) (12/88) and Kaufman et al., U.S. Pat. No. 5,451,521 (9/95)..

The EP reference discloses a factor 8 derivative compound and pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689: wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The EP reference differs from the presently claimed invention by failing to recite the Arg-740 mutation (e.g. Arg to Ala) and the use of a spacer which comprises a B-domain peptide.

However, the Kaufman reference discloses the making of procogulant factor VIII derivatives of formula A-X-B wherein A is 1-372 and B is 1690-2332 and X is a linking moiety which may comprise 0-1316 amino acids especially those amino acids selected from the sequence Arg-372 to Ser-1690 with a preferred embodiment incorporating Arg 372-Arg740 (e.g. see col. 8-9). Thus, Kaufman provides motivation to the skilled artisan to attach the A1-A2 heavy chain fragment to the light chain C1-C2 fragment utilizing amino acid linkers derived from the B chain of any length; of which is not critical. The Kaufman reference further teaches the replacement of Arg residues at position 740 (e.g. see Abstract) with non-conservative amino acid substitutions, including Ile, in order to obtain proteolytic resistance (e.g. see col. 2, lines 40-67 and Table II in

col. 9). Accordingly, the substitution of Arg 740 with other nonconservative amino acids which possess similar side chain properties to Ile (e.g. aliphatic non-charged e.g. nonpolar), such as alanine or valine would have been obvious to one of ordinary skill in the art who wishes to obtain further proteolytic resistant derivatives. Thus, the modification of the EP reference peptide to incorporate a linking peptide which comprises B-chain residues and the further substitution of Arg with aliphatic non-charged amino acid residues (e.g. Ile, Val or Ala) would have been obviious in view of the teaching of the Kaufman reference to use such modifications in order to make procoagulant proteins.

Accordingly, the EP reference combined with the Kaufman reference render obvious proteins within the scope of the presently claimed invention. Accordingly, the above reference(s) meet the critical chemical claim limitations (e.g. absence of a B domain and Vwf binding site; and presence of a linking amino acid) and possesses improved properties and thus would be expected to possess the same conformational structure upon thrombin activation as presently claimed. See MPEP 2112.02 and *In re Spada*, 15 USPQ2d 1655,1658 (Fed. Cir. 1990)("Products of identical chemical composition can not have mutually exclusive properties"). The Examiner lacks the facilities to test reference protein (s) to see if it meets functional limitations; thus placing the burden directly on applicant (e.g. See *In re Brown*, 173 USPQ 685,688 (CCPA 1972)) .

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons. The above rejection was modified in response to applicant's amendment (e.g. to encompass newly added claims). Applicant first intimates that the above 103 rejection somehow conflicts with the 102 rejection with regard to the sequence spacer. The Examiner disagrees since the claimed invention can be interpreted to encompass an Arg mutation which also serves as the spacer, or alternatively the presence of a spacer separate and apart from the "Arg" mutation. Applicant's argument that the references taken separately fail to render obvious the presently claimed invention, is not germaine to the obviousness rejection above which is directed to the combined teaching of both references. Applicant fails to provide a

reason why one of ordinary skill wouldn't combined the above two references to obtain multiple proteins species within the scope of the presently claimed invention. Applicant further argues that the references fail to teach functional/conformational characteristics of the protein upon thrombin activation. With regard to to applicant's functional/conformational limitation language it is noted that functional activity would necessarily flow from a compound that possesses chemical structure within the scope of the presently claimed invention; unless demonstrated otherwise. Accordingly, the above rejection, as modified, is hereby retained.

*New **Rejection***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17 and 107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (e.g. New Matter Rejection).

Applicant's newly added functional/conformational limitation is clearly broader than that described on page 9, line 6-11 which is limited to thrombin activation, with the further description of the covalent association of the A2 domain with the light chain..

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa

June 27, 1999